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TITLE: The University of Utah Clinical Genetics Research Program as an NF1 Consortium Site

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14. ABSTRACT

The University of Utah Clinical Genetics Research Program (CGRP) provided the infrastructure for our site to perform clinical trials within the scope of a consortium to treat multiple medical complications of neurofibromatosis type 1. The U of Utah site executed aims of the overall consortium by attending 2 meetings of the consortium (November, 2005 and April, 2006), participating in all teleconference calls, and active engagement in the development and submission of a clinical trials application to the Department of Defense in August, 2006. David Viskochil served as vice-chair of the Biology Committee, and he organized a symposium of investigators and clinicians who were part of a MPNST (malignant peripheral nerve sheath tumor) Consortium and the MPNST Committee of the NF1 Consortium that convened as a satellite meeting of the full NF1 Consortium meeting in Atlanta in April, 2006. A study coordinator has been hired through the CGRP at the U of Utah to assist in the development of material submitted in the clinical trials grant proposal. No data has been collected.

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INTRODUCTION

This research encompassed the development of the University of Utah as a collaborating site within an NF1 Consortium. There are 8 other sites and an operations center at the University of Alabama, Birmingham. The U of Utah was funded in conjunction with the other sites in early November, 2005. As part of the original proposal we composed a clinical trial to assess spine abnormalities, which was presented at the inauguration meeting that was held in Baltimore in November, 2006. We also composed a 1-page abstract which was presented to other members of the consortium. After the initial meeting, we participated in teleconference calls, and members of our site enrolled in various committees charged with the development of clinical trials. A total of 4 clinical trials committees were established (plexiform neurofibroma, learning problems, malignant peripheral nerve sheath tumors, and optic nerve pathway tumors). The U of Utah proposal for spine abnormalities in NF1 was not adopted as a potential clinical trial for the anticipated first grant proposal anticipated for submission in 2006. David Viskochil attended a second meeting held in Atlanta in April of 2006 to formalize the selection for the development of 2 full clinical trials, plexiform neurofibroma and learning problems. David Viskochil also organized an MPNST consortium meeting as a satellite meeting of the NF1 Consortium meeting in Atlanta. It signified a transfer of information from MPNST consortium members to the MPNST committee members of the NF1 Consortium. In Spring of 2006 we hired a study coordinator to help develop and implement clinical trials related to the NF1 Consortium submission anticipated in 2006. Finally, David Viskochil expanded his effort to include serving as co-chair of the Biology committee of the NF1 Consortium. The proposal to conduct 2 clinical trials and support the infrastructure to carry out these trials was submitted by Dr. Jeanette Lee (U of Alabama, Birmingham) in August, 2006. Members of the U of Utah NF1 consortium site continued to discuss and plan for the anticipated approval of at least 1 clinical trial. The site project funding ended prior to the initiation of the clinical trial, nevertheless the U of Utah has retained the services of the study coordinator by institutional bridge funding until final disclosure is publicized with respect to funding of a clinical trial through this NF1 Consortium.

BODY (based on statement of work outlined in the original proposal)

Task 1. Develop Clinical Protocols for the Consortium (Months 0-12):

a. Expand in detail the proposed clinical protocol to present at consortium planning meeting.
b. Attend Consortium planning meeting for selection of clinical protocol(s).
c. Write sections of FY06 NF Consortium Awards proposal.

David Viskochil and David Stevenson attended the initial NF1 Consortium Planning meeting held in Baltimore in November, 2005. We presented 2 proposals for review by the principal investigators from the additional sites. The titles were; MPNST in NF1 and Osseous Abnormalities in NF1. The powerpoint presentation composed for that discussion is appended. At the initial planning meeting 4 committees were developed corresponding to 4 separate clinical manifestations of NF1 deemed amenable to development and implementation of clinical trials through this consortium. These included plexiform neurofibroma, MPNST, optic nerve pathway tumor, and learning problems (cognition).

The NF1 Consortium planning meeting for selection of clinical protocols was held in Atlanta in April, 2006. With due deliberation, the Governing Body selected clinical trials proposals to treat plexiform neurofibroma with rapamycin and learning problems with lovastatin. There were 2 concept trials that were also voted to be included in a grant proposal for funding the clinical trials, for MPNSTs and Optic Nerve Pathway Tumors. Prior to this meeting there were bimonthly conference calls between the principal investigators from each site and committee chairs to be informed of progress on protocols from each of the 4 clinical trials committees. In addition, separate committee conference calls were held on a routine basis.

Sections of the FY06 NF Consortium Awards proposal were written and reviewed by David Viskochil and David Stevenson. David Viskochil served on the MPNST and OPG committees. He also was responsible

for compiling the patient profile for the U of Utah site. He served on the Biology Committee as co-Chair. David Stevenson served on the plexiform neurofibroma committee. John Carey, co-director of the NF Clinic at the U of Utah, served on the Learning Disabilities and Cognition Committee. Other members of the U of Utah site who agreed to serve on committees included Dr. Robert Ward, pediatric pharmacologist, on the Pharmacology Committee and Dr. Kevin Moore, pediatric neuroradiologist, on the Radiology Committee.

Task 2. Development of NF1 Project Database (Months 0-12):

a. Continue to develop a web site for data management and subject recruitment of NF1 individuals through collaborations with Bernie LaSalle (Informatics Core Director at the GCRC).
b. Input data from physical examinations and medical histories on NF1 exam forms from individuals enrolled in NF1 Registry.
c. Test transfer of data from outside institutions included in the Consortium.
d. Test transfer of digital images from radiographic imaging modalities from outside institutions included in the Consortium.

The U of Utah NF1 consortium site has worked with Bernie LaSalle, director of the informatics in the General Clinic Research Center, in ongoing development of a database for multiple clinical studies. Unrelated to the U of Utah consortium site project, he is actively engaged in developing a website for the collection of subjects under a multi-center trial to study the spine abnormalities in NF1 children. There are additional studies that have been integrated into this database, including bone health studies of NF1 children. To date, approximately 110 subjects have been enrolled and all have agreed to be contacted about future clinical trials and studies.

All subjects entered into the NF1 databases have been enrolled through the Clinical Genetics Research Program in the GCRC. This enrollment includes performance and documentation of a physical examination and obtaining pertinent medical records. The Clinical Genetics Research Program is comprised of 3 study coordinators who are supervised by David Viskochil. Heather Hanson is a study coordinator who has devoted a portion of her effort to the recruitment of NF1 subjects and is the lead coordinator for clinical trials related to the NF1, including the NF1 Consortium.

We have not had the opportunity to transfer data or imaging from other sites in the NF1 Consortium. However, the NF database and website that is almost completed will have this capability. We have demonstrated in other NF1-related studies that our site can transfer data and images to other academic institutions. This was clearly shown in our collaboration with Dr. Bruce Korf (PI) in the Natural History of Plexiform Neurofibroma study, which is funded by the NF Program of the Department of Defense.

Task 3. Plan Development and Institutional Review (Months 0-12):

a. Train a clinical coordinator to set up infrastructure to identify potential subjects and contact appropriate providers to offer enrollment within the institution.
b. Refine infrastructure to arrange requests, procedures and transfer of prospectively acquired tissue from outside institutions.
c. Assure compliance with USAMRMC and home institutional guidelines on research involving human subjects.

The Clinical Genetics Research Program at the U of Utah has been active since 1998, and one goal of the study coordinators is to maintain IRB approvals and enroll subjects for myriad studies related to genetics. There are 3 coordinators who oversee approximately 20 IRB protocols from 7 principal investigators. They also collect *ad hoc* families through the phenotyping core for various faculty members. Heather Hanson has taken on oversight of the NF1-related protocols in the CGRP. She has also interacted with the Shriners Intermountain Hospital study coordinators who are enrolling NF1 subjects for 3 separate bone studies. Included in these studies is the implementation of a bone tissue bank facility for the Shriners Hospital Network. Ms. Hanson has

collaborated with Shriners coordinators in the procurement and processing of this bone material. She has helped transfer some tissue items to David Viskochil's laboratory for molecular analysis. Ms Hanson oversees the IRB protocols for NF1 subjects, and she is aware of all guidelines related to the appropriate enrollment of human study subjects. She interacts with clinical geneticists and orthopedists at 3 facilities in Salt Lake City to identify potential study participants.

KEY RESEARCH ACCOMPLISHMENTS

The primary goal of the U of Utah site was to work in a collaborative way to help procure funding for clinical trials in the context of an NF1 Consortium. A key accomplishment was the development of 2 clinical trials that were embedded in a grant proposal (NF 060016) that was submitted to the Department of Defense 2006 Neurofibromatosis Program in August, 2006.

An unexpected key research accomplishment was a symposium that linked investigators from an MPNST consortium funded by the DoD NF Program (NF 030073) as a Clinical Trials Development Award (CTDA) with investigators who comprised the MPNST Committee of the NF1 Consortium. The symposium was organized by David Viskochil to explore the goals of 1 of the CTDA-designed studies (identify risk factors for the development of MPNST in NF1) for potential incorporation into clinical trials for MPNST treatment developed through the NF1 Consortium. The symposium was held on April 6, 2006 in conjunction with the NF1 Consortium Meeting that was held on April 7, 2006 in Atlanta. In addition to members of the MPNST Committee of the NF1 Consortium and members of the MPNST Consortium from the CTDA, Dr. Larry Baker from SARC (Sarcoma Alliance for Research through Collaboration) joined us to review progress by CTDA investigators and inform the attendees about the infrastructure of SARC. Attendees to this meeting are bolded in the list below.

MPNST Committee of the NF1 Consortium

Chairs:
John Perentesis, University of Cincinnati (john.perentesis@cchmc.org)
Karen Albritton, Harvard University (karen_albritton@dfci.harvard.edu)

Pablo Arnoletti, University of Alabama, Birmingham (Pablo.Arnoletti@ccc.uab.edu)*
David Gutmann, Washington University (gutmannd@neuro.wustl.edu)*
Martin Nicholas, University of Chicago (mnichola@neurology.bsd.uchicago.edu)*
Roger Packer, Childrens National Medical Center, Washington, DC (rpacker@cnmc.org)*
Terrence Peabody, University of Chicago (tpeabody@surgery.bsd.uchicago.edu)*
Arie Perry, Washington University (apry@pathology.wustl.edu)*
John Pressey, University of Alabama, Birmingham (JPressey@peds.uab.edu)*
James Tonsgard, University of Chicago (tonsgard@midway.uchicago.edu)*
David Viskochil, University of Utah (dave.viskochil@hsc.utah.edu)
Brian Weiss, University of Cincinnati (brian.weiss@cchmc.org)
Brigitte Widemann, NCI, Pediatric Branch, Bethesda (widemanb@mail.nih.gov)
Jeannette Lee, University of Alabama, Birmingham (jylee@uab.edu)
Karen Cole, University of Alabama, Birmingham (Karen.Cole@ccc.uab.edu)*

MPNST Consortium from the Clinical Trials Development Award (DoD)

Rosalie Ferner, Guys and St. Thomas Trust, London, UK
Jan Friedman, University of British Columbia, Vancouver, CA
Arie Perry, Washington University*

David Viskochil, Univeristy of Utah
Brigitte Widemann, NCI, Pediatric Branch

Ad hoc Invitees

Laurence Baker, University of Michigan (SARC)
Karen Cichowski, Harvard University
Shyra Miller, University of Cincinnati

Dr. Jeannette Lee is the PI for the NF1 Consortium Operations Center. She oversaw the submission of the Clinical Trials Proposal that was submitted in August, 2006 in response to a Program Announcement by the DoD NF Program. The chairs for the MPNST Committee of the NF1 Consortium are Drs. John Perentesis and Karen Albritton. Drs. Karen Chichowski and Shyra Miller are ad hoc attendees who gave presentations to the group. The agenda for the meeting is provided below:

AGENDA

0930 Introductions; past history of MPNST consortium - D Viskochil
1000 Summary of MPSNT protocol(s) for the NF1 Consortium - J Perentesis
1030 Epidemiology of MPNST in NF1 - J Friedman
1100 Diagnostic Imaging of MPNST and Plexiform neurofibromas - R Ferner
1130 Clinical Trial of Neoadjuvant Therapy in NF1 - B Widemann
1200 SARC - L Baker
1230 Lunch
1300 Ras-neurofibromin Signal Transduction Pathway - K Cichowski
1330 Gene Expression Patterns in Peripheral Nerve Sheath Tumors – S Miller
1400 Immunohistochemical Patterns in PNSTs – D Viskochil
1430 Break
1500 Open Discussion on Potential Protocols

Anticipated Meeting Outcomes (stated as agenda items)

Identify potential biologic agents for future clinical trials
Specify primary and secondary endpoints for MPNST treatment protocols
Identify limitations of NF1 Consortium and Operations Center in MPNST Trials
List collaborative agencies that could facilitate NF1 MPNST Trials
Identify mechanisms to enroll MPNST and control subjects into longitudinal registries

At the conclusion of the meeting the attendees had addressed the above agenda items. A major outcome was the identification of 2 unique signaling pathway targets for MPNST treatment protocols, Erk in the mitogen activated protein kinase pathway and mTOR. The endpoints for treatment protocols were accepted as survival and tumor response by volume loss. Limitations of multi-center trials were described, and attendees acknowledged the value of consortia to enroll and complete data acquisition with due respect for safety monitoring. Presently, the 2 collaborative agencies that are prepared to facilitate NF1 MPNST trials were identified as the NF1 consortium and SARC. Mechanisms to enroll patients and controls for longitudinal registries were viewed as intimately tied to the roll-out of protocols for treatment of NF1-associated MPNSTs.

Over the course of the ensuing months Drs. Brian Weiss and Brigitte Widemann worked closely with the chairs to develop a clinical trial for MPNST that was included in the DoD proposal submitted by Dr. Lee for 4 clinical trials. The MPNST trial was embedded in section 8 of the proposal, and the primary hypothesis which evolved in part from the April meeting states: Targeted inhibition of signaling pathways upstream and downstream of the Ras/NF1 pathway (e.g. Raf, P13K, RalGEF) will effectively and selectively inhibit the

growth and progression of NF1-related MPNST. The primary specific aim to address this hypothesis is: To determine if combination multikinase inhibitors and chemotherapy will be effective in treating children with NF1 and relapsed MPNST. This protocol is tied to those individuals who have entered and not responded to Dr. Widemann's protocol (PHASE II TRIAL OF NEOADJUVANT CHEMOTHERAPY IN SPORADIC AND NEUROFIBROMATOSIS TYPE 1 ASSOCIATED HIGH GRADE UNRESECTABLE MPNSTs), and demonstrates the value of linking the SARC infrastructure with the NF1 Consortium.

CONCLUSIONS

This project has been successful in its contribution to the NF1 Clinical Trials Consortium. Members from the U of Utah site collaborated in committee deliberations and help complete a proposal for funding of 2 clinical trials to treat significant manifestations of NF1, plexiform neurofibroma and learning problems. In the process, this study has established an increased presence for NF1-related research in the Clinical Genetics Research Program. In addition, families with NF1 throughout the Mountain West region are now familiar with potential clinical trials that may be carried out at the University of Utah. Finally, this project has provided a conduit for ideas developed through a Clinical Trials Development Award (NF 030073) to the MPNST Committee of the NF1 Clinical Trials Consortium.

University of Utah, Salt Lake City

Primary Children's Medical Center
General Clinical Research Center
Clinical Genetics Research Program
Intermountain Shriners Hospital
Huntsman Cancer Institute

David Viskochil, MD, PhD – Principal Investigator
Professor of Pediatrics; Director Division of Medical Genetics
David Stevenson, MD – Co-Investigator
Instructor of Pediatrics
John Carey, MD, MPH – Co-Investigator
Professor of Pediatrics
Jacques D'Astous, MD; Department of Orthopedics and Shriners Hospitals
Holly Zhou, MD; Department of Pathology and PCMC Pathology Services
Heather Hanson – Research Coordinator
Bernard LaSalle – Director of Informatics, GCRC

Expertise in NF1 Clinical Research

- Skeletal Abnormalities
  - Tibial dysplasia and pseudarthrosis
  - Spine abnormalities and dystrophic scoliosis
- Peripheral Nerve Sheath Tumors
  - Immunohistochemistry
  - Somatic genome analysis of tumors
  - Natural history
- Optic pathway tumors
  - COG protocols
  - Imaging and visual evoked responses
- Gene Characterization
  - Mutation analysis
  - Genomic sequencing

Tibial dysplasia

Clinical outcomes study (1/04-12/08)

- Funded by Shriners Research Foundation
- PI – John Carey (co-inv: Viskochil & Stevenson)
- Specific Aims:
  - To assess health status and health-related quality of life (HRQL) in children and adolescents with NF1 and tibial dysplasia (TD)
  - To assess outcome in 100 adult patients with NF1 who are diagnosed with tibial dysplasia in childhood
  - To assess the natural history and short-term outcome of a cohort of at least 60 children with NF1 diagnosed with TD and at least 60 children with TD without NF1
- Development of the Intermountain Shriners Hospital NF1 Orthopedic Core Facility (NOCF)

Tibial Dysplasia

- Research Award (1/05-12/06)
  - Funded by the Shriners Research Foundation
  - PI – David Viskochil
  - Specific Aims:
    - To determine the histologic, immunohistochemical and biochemical profiles of cellular material derived from tibial pseudarthrosis specimens, and delineate differences between NF1-related and sporadic cases
    - To determine if cellular material from tibial pseudarthrosis tissue harbor somatic mutations of the *NF1* gene
  - Full utilization of the NF1 Orthopedic Core Facility developed at the Intermountain Shriners Hospital

Bone Health in NF1

- Innovative Research Award (7/03-6/06)
  - Funded by PCMC Research Foundation
  - PI: David Stevenson (mentor – Viskochil)
  - Specific aims:
    - Assess bone health by DXA, pQCT, and serum indices in 100 individuals with NF1 between 5 and 18 years of age
    - Identify distinctive *NF1* mutation classes between individuals with and without bone abnormalities in this NF1 cohort (genotype-phenotype correlation)
  - Developed strong liason between the clinical genetics research program (phenotype core) and the GCRC
  - Led to K23 award for Dr. Stevenson

Osseous Abnormalities in NF1

- K23 Clinical Research Training Award
  - NIH/NINDS (08/05-06/10)
  - PI: David Stevenson (Co-mentors: Viskochil & Carey)
  - Specific Aims:
    - Determine the differences in bone-health variables between NF1 individuals and individuals without NF1, and between NF1 individuals with and without osseous abnormalities
      Determine genotype-phenotype correlations of the *NF1* gene and osseous abnormalities
    - To assess health status and health-related quality of life (HRQL) in children and adolescents with NF1 and scoliosis
  - 85% protected time to perform this research
  - Integrated with phenotype core (CGRP)

Spine Abnormalities

- Clinical Outcomes Study (1/06-12-09)
  - Funded by Shriners Research Foundation
  - PI: Jacques D'Astous (Co-inv: Viskochil & Carey)
  - Specific Aims:
    - To assess health status and health-related quality of life (HRQL) in children and adolescents with NF1 and scoliosis
    - To assess the natural history and short-term response to therapy in a cohort of children with NF1 and scoliosis prospectively diagnosed during the course of the four-year study period
    - To assess biochemical markers of bone metabolism in NF1 individuals

Spine Abnormalities

- Pending proposal to NIH/NINDS
- PI: Viskochil
  - Co-PI: Elizabeth Schorry (U. of Cincinnati)
  - Co-PI: Jan Friedman (U. British Columbia)
  - Co-PI: Zulf Mughal (U. of Manchester, UK)
- Specific Aims:
  - Identify associations of spinal cord dural ectasias, spinal neurofibromas, and meningoceles with dysplastic osseous abnormalities and dystrophic scoliosis in individuals with NF1
  - Define the clinical history and short-term outcome of dystrophic scoliosis, and describe a cohort of individuals with NF1 with respect to various radiographic indices associated with dystrophic scoliosis
  - Determine the differences in bone-health variables between individuals with versus without NF1, and between NF1 individuals with versus without dystrophic scoliosis

Institutional Expertise - personnel

- Orthopedics
  - J. D'Astous: spine abnormalities
  - J. Smith: titanium rib for dystrophic scoliosis
  - P. Stevens: tibial dysplasia and gait lab
- Oncology
  - L. Randall: surgical oncologist for PNSTs
  - C. Bruggers: optic pathway tumors and low-grade gliomas
  - N. McCallister: sarcomas
- Pathology
  - C. Coffin: soft tissue tumors in pediatrics
  - H. Zhou: peripheral nerve sheath tumors
- Genomics
  - R. Weiss: high-throughput sequencing
  - L. Jorde: haplotype analysis of the NF1 locus
  - A. Brothman: comparative genomic hybridization, microarray
- Psychology
  - N. Cantor: psychological testing
  - W. McMahon: psychiatric evaluations, behavior studies
- Radiology
  - K. Moore: peripheral nervous system imaging

Institutional Expertise - programs

- Clinical Genetics Research Program – phenotype core
- General Clinic Research Center (GCRC)
- Huntsman Cancer Institute (HCI)
- Shriners Intermoutain Hospital
- Lysosomal Storage Disorder (LSD) Treatment Center
- The Center for Pediatric Nutrition Research (CPNR)
- The Biochemical Genetics Laboratory at ARUP
- Utah Center for Genome Research
- Cytogenetics Research & Development Laboratory
- John A. Moran Eye Center
- Utah Autism Research Program
- Utah Population Database

NF1 Population

- Intermountain West Region
  - Utah, Idaho, Wyoming, Nevada, Montana
  - Western Colorado, Northern Arizona, Eastern Oregon
- NF Clinic follows about 400 individuals and ~150 families are seen annually
- Utah has highest birth rate - ~50,000/year
- Average household size is 3.13 in Utah (US=2.59)
- 130 individuals are enrolled in the INNFFDB
- 85 individuals (5-18) are enrolled in study - Skeletal Phenotyping and Mutation Screening in NF1
- 12 individuals enrolled in study – Natural History of Plexiform Neurofibromas
- CTF/NNFF Chapter – established since 1984

Proposals

- **MPNST in NF1**
  - MPNST Consortium
    - Multicenter and multidiscipline starting with symposium in London in 2000.
    - High input from Ferner, Friedman, Perry, Viskochil and Widemann over last 3 years
  - One of 3 Clinical Trials
  - Links Sarcoma Centers with NF1 Centers
- **Osseous Abnormalities in NF1**
  - Derived from K23 award (David Stevenson – PI)
  - Links Shriners Hospitals with NF1 Centers

Proposed Study – MPNST in NF1

Primary objective

Identify a set of clinical, genetic, molecular and environmental factors that identify those individuals with NF1 who are at highest risk to develop MPNSTs. We will use a cross-sectional case-control protocol to determine differences between individuals with NF1 who have MPNST versus those without MPNST.

Developed by Jan Friedman (UBC), Ros Ferner (Guys & St. Thomas Trust), Brigitte Widemann (NCI), Arie Perry (Washington U), and David Viskochil (U. of Utah) through DAMD-NF030073 (2/2004 – 03/2006) - *Malignant Peripheral Nerve Sheath Tumors in Neurofibromatosis Type 1: A Multicenter Project with 3 Clinical Trials*

Proposed Study – MPNST in NF1

- **Hypotheses:**
  - Individuals with NF1 who have higher "tumor burden" are at higher risk to develop MPSNT.
  - Individuals with NF1 who either have a family history of sarcoma or have been exposed to therapeutic radiation, or have a neuropathy are at high risk to develop MPSNT.
  - Individuals with NF1 whose mutation is a whole-gene deletion are at higher risk to have an MPNST than those who do not have a whole-gene deletion.

Proposed Study – MPNST in NF1

Relevance

Individuals with neurofibromatosis type 1 (NF1) are at a relatively high risk to develop a deadly sarcoma called malignant peripheral nerve sheath tumor (MPNST) that has a 5-year survival of about 25%. Earlier detection and appropriate treatment predicts less morbidity and less mortality. Presently, it is difficult to diagnose MPNST at an early stage in disease. The identification of a cohort of individuals with NF1 who may be at high risk for MPNST would enable health care practitioners to establish rigorous screening protocols for early detection of MPSNT in NF1.

Proposed Study – MPNST in NF1

- **Specific aims:**
  - To determine if "tumor burden" is higher in those individuals with NF1 who develop MPNST, and, if so, estimate a relative risk to develop MPSNT based on "tumor load".
  - To identify historical factors that correlate with altered relative risk to develop MPNST in NF1.
  - To identify molecular factors that correlate with altered relative risk to develop MPNST in NF1.

Proposed Study – MPNST in NF1

- **Study Population:**
  - Aim 1
    - 100 subjects with NF1 and MPNST
    - 300 subjects with NF1 without MPNST
  - Aim 2
    - Extended pedigree analysis of family cancer history in subjects enrolled in aim 1 – all family members with cancer (with and without NF1)
  - Aim 3
    - Biological sampling to be performed on all subjects with MPNST (blood, serum, tumor)
    - Serum, urine, and DNA sampling on subjects without MPNST

Proposed Study – MPNST in NF1

Design/Methodology

Cross-sectional, case-control study is designed and powered to enable us to accept or reject our primary hypothesis that a subgroup of individuals with NF1 can be identified who are at higher risk to develop MPNST.

After providing informed consent, each subject (case or control) will undergo extensive clinical phenotyping. This phenotype analysis includes the following:

- detailed medical history, including exposures to environmental agents
- three-generation family history, with focus on cancers
- detailed physical examination using a standard protocol to quantify NF1 manifestations
- whole-body MRI scan (axial scan from neck to distal thigh at 10-mm slices as STIR)
- Collection of biological materials (tumor, blood, serum, urine)

Proposed Study – MPNST in NF1

- **Endpoints for AIM 1:**
  - Determine correlation between the development of MPNST and volume of internal peripheral nerve sheath tumors, as measured by volumetric "whole-body" MRI
  - Determine correlation between the development of MPSNT and type and/or number of discreet neurofibromas; dermal, subcutaneous, and plexiform
  - correlation between the development of MPSNT and the presence or absence of optic pathway tumor, presence and number of discreet T2-weighted hyperperintense nodules, and presence of intracranial glioma.

Proposed Study – MPNST in NF1

- **Endpoints Aims 2 & 3:**
  - determine if family history of cancer, specifically sarcoma, is associated with a higher relative risk to develop MPNST in NF1
  - determine if history of radiation exposure or medicinal therapy correlates with increased relative risk to develop MPSNT in NF1
  - determine the relative risk for MPNST in those who have an *NF1* whole-gene deletion
  - establish and maintain a tissue repository for MPNST, tumor DNA, white blood cell DNA, serum, and urine for future studies to identify biomarkers that demonstrate differences between individuals with NF1 who have MPNST versus plexiform neurofibroma versus no tumor

Proposed Study – MPNST in NF1

- **Timeline:**
  - Development of infrastructure to prospectively identify individuals with NF1 and MPNST – 9 months
  - Active recruitment with high surveillance of the MPNST and NF1 population:
    - 25 subjects per year X 4 years
    - 35 subjects per year X 3 years
  - Recruitment of age- and sex-matched controls from the developed infrastructure as MPSNT subjects are identified
  - Tumor biology evaluated as the tumors arrive
  - Biologic assays for non-tumor specimens for both MPNST and NF1 control cohorts performed after subject enrollment
  - Final data analysis – after subject recruitment and assays of non-tumor biological specimens completed – 6 months
  - Study completed in 4-5 years

Proposed Clinical Study – Osseous abnormalities in NF1

Objectives

- Explore the hypothesis that NF1 is a constitutional disorder of bone with generalized osseous abnormalities.
- Identify genotype-phenotype correlations to determine if genotype is a prognostic factor for the predisposition of osseous abnormalities.
- Establish a multi-center study to evaluate the burden of morbidity and clinical outcome of scoliosis in NF1.

Proposed Clinical Study – Osseous abnormalities in NF1

Clinical/Therapeutic Relevance

Spinal and osseous abnormalities are highly morbid in NF1, and not well understood. A great deal of new information will be needed in order to guide new research and develop effective medical therapies for these disabling disorders. The specific aims in this study will help to understand the pathogenesis and clinical history of spinal abnormalities in NF1, and identify effective screening and outcome modalities for treatment.

Proposed Clinical Study – Osseous abnormalities in NF1

- **Study Population**
  - 150 Individuals with NF1 between 5-20 years
    - No bone abnormalities
    - Tibial pseudarthrosis
    - Scoliosis
  - 80 Families with a parent with NF1 and 2 affected offspring, at least 1 with an osseous abnormality
  - 50 individuals with NF1 and scoliosis with age- and sex-matched individuals with NF1 without scoliosis

Osseous abnormalities in NF1

- **Study Design for specific aim 1** - **Determine the differences in bone-health variables between individuals with and without NF1, and between NF1 individuals with and without osseous abnormalities.**
  - Enroll 150 NF1 subjects between 5 and 20 years of age
  - Perform the following studies:
    - Routine phenotype analysis – score for osseous abnormality
    - DXA imaging
    - Peripheral quantitative computerized tomography (pQCT)
    - Scoliosis imaging
    - Biochemical markers
  - Compare values against historical age-, sex-matched healthy controls without genetic conditions or disease.
  - From this group of 150; identify a cohort of NF1 subjects with osseous abnormality versus those who definitely do not have an osseous abnormality
  - Compare differences of bone health between these 2 NF1 groups

Proposed Clinical Study – Osseous abnormalities in NF1

- Study Design for specific aim 2 - **Determine genotype-phenotype correlations of the *NF1* gene and osseous abnormalities.**
  - Cohort of 150 subjects with NF1 from specific aim 1 will undergo *NF1* mutation analysis
  - Anticipate 30 with osseous abnormality; *NF1* mutation classes will be assessed between the osseous group versus non-osseous group.
  - Enroll 80 families with an affected parent and 2 affected offspring with at least 1 child having an osseous abnormality.
  - Obtain DNA for haplotype analysis
  - assess if the *NF1* haplotype from the unaffected parent contributes to the osseous abnormality

Proposed Clinical Study – Osseous abnormalities in NF1

- Study Design for specific aim 3 - **To assess health status and health-related quality of life (HRQL) in children and adolescents with NF1 and scoliosis.**
  - **200 individuals with NF1 will be enrolled throughout North America (50 with scoliosis and 150 without scoliosis)**
  - **Data to be collected at time of enrolment come from:**
    - demographic questions and medical records
    - NF1 criteria and severity cover sheet
    - NF1 Core questions
    - general orthopedic questions
    - Radiographs
    - Health-Related Quality of Life (HRQL) questionnaire
    - Functional Health Status (FHS) questionnaire
  - **Annual assessment x 3**
  - a linear mixed model (Laird and Ware, 1982) with available data from all subjects will be used as the primary analysis approach

Proposed Clinical Study – Osseous abnormalities in NF1

- **Endpoints**
  - Bone-health measurements for NF1 vs. controls
  - Bone-health measurements for NF1 with and without osseous abnormalities
  - Haplotype analysis to detect contribution of the normal NF1 allele to the osseous phenotype
  - Natural history and quality of life instruments for NF1 subjects with versus without scoliosis

Proposed Clinical Study – Osseous abnormalities in NF1

- **Time Line**
  - 9 months for infrastructure development
  - 1 year for intense recruitment
  - 4 years for data acquisition
  - 6 months for data analysis

With overlap and shortened infrastructure development and enhanced recruitment this would be a 4-year study